

Gonorrhoea

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ABSTRACT

INTRODUCTION: In 2012, the diagnosis rates for gonorrhoea among adults aged 20 to 24 years in the UK were 249 per 100,000 for men and 140 per 100,000 for women. Resistance to one or more antimicrobial agent is reported in more than one quarter of isolates. Co-infection with *Chlamydia trachomatis* is reported in 10% to 40% of people with gonorrhoea in the US and UK. **METHODS AND OUTCOMES:** We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of treatments for uncomplicated infections in men and non-pregnant women, and in pregnant women? What are the effects of treatments for disseminated gonococcal infection? What are the effects of dual treatment for gonorrhoea and chlamydia infection? We searched: Medline, Embase, The Cochrane Library, and other important databases up to September 2013 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). **RESULTS:** We found 7 studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. **CONCLUSIONS:** In this systematic review we present information relating to the effectiveness and safety of the following interventions: antibiotic regimens (dual treatment, multiple dose, single dose).

QUESTIONS

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What are the effects of dual treatment for gonorrhoea and chlamydia infection?	8


INTERVENTIONS

TREATMENT IN MEN AND NON-PREGNANT WOMEN

 Likely to be beneficial


Single-dose antibiotic regimens in men and non-pregnant women† 4

TREATMENT IN PREGNANCY

 Likely to be beneficial

Single-dose antibiotic regimens in pregnant women† 6

DISSEMINATED GONORRHOEA

 Likely to be beneficial

Multidose antibiotic regimens for disseminated gonorrhoea* 8

GONORRHOEA AND CHLAMYDIA

 Likely to be beneficial

Dual antibiotic treatment for gonorrhoea and chlamydia* 8

Footnote

† Based on results in individual arms of RCTs and observational studies.

* Based on non-RCT evidence and consensus.

Key points

- Gonorrhoea is caused by infection with *Neisseria gonorrhoeae*. In men, uncomplicated urethritis is the most common manifestation; while in women, less than half of cases produce symptoms (such as vaginal discharge and dyspareunia).

Rates of diagnosed gonorrhoea infection in the UK rose by more than 70% between 2008 and 2012. This may be, in part, explained by improved diagnostic techniques.

In 2012, the diagnosis rates for gonorrhoea among adults aged 20 to 24 years in the UK were 249 per 100,000 for men and 140 per 100,000 for women.

Rates are highest in adults aged 20 to 24 years.

Resistance to single-dose antimicrobials develops frequently, and antimicrobial sensitivity of gonococcal isolates is monitored nationally to monitor and inform prescribing guidelines.

Co-infection with *Chlamydia trachomatis* is reported in 10% to 40% of people with gonorrhoea in the US and UK.

- Single-dose antibiotic regimens have achieved cure rates of 95% and higher in men and non-pregnant women with urogenital or rectal gonorrhoea, although we don't know how different single-dose antibiotic regimens compare with each other.

Single-dose antibiotics are also effective for curing gonorrhoea in pregnant women.

- In people with disseminated gonococcal infection, there is consensus that [multiple-dose regimens](#) using cephalosporins or fluoroquinolones (when the infecting organism is known to be susceptible) are the most effective treatments, although evidence supporting this is somewhat sparse.
- We found insufficient evidence to judge the best treatment for people with both gonorrhoea and chlamydia, although theory, expert opinion, and clinical experience suggest that a [combination of antimicrobials](#) active against both *N gonorrhoeae* and *C trachomatis* is effective.

Clinical context

GENERAL BACKGROUND

Untreated or inadequately treated gonorrhoea can lead to infection of the upper genital tract, with the potential complications of pain, infertility and ectopic pregnancy. The incidence of gonorrhoea increased by 15% in the UK between 2012 and 2013. There is increasing awareness of the danger of gonorrhoea becoming an untreatable infection due the emergence of antimicrobial resistance.

FOCUS OF THE REVIEW

This review looks at the evidence for the effectiveness of single dose and antimicrobial treatment in the treatment of simple and disseminated infection with *Neisseria gonorrhoeae*. It also examines the evidence for simultaneous treatment of *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. It does not comment on the effectiveness of individual antimicrobial regimens as this decision is informed by local surveillance reports.

COMMENTS ON EVIDENCE

There is little published data in the form of RCTs, as much of the data relies on demonstration of microbial cure as proof of effectiveness and placebo controlled RCTs would be unethical given the clear demonstration of microbial cure. Further, although there is considerable evidence of resistance patterns from national surveillance programs, these data are ineligible for inclusion in the benefits and harms sections of this review as they are not RCT data.

SEARCH AND APPRAISAL SUMMARY

The update literature search for this review was carried out from the date of the last search, March 2010 to July 2013. For more information on the electronic databases searched and criteria applied during assessment of studies for potential relevance to the review, please see the Methods section. Searching of electronic databases retrieved 79 studies. After de-duplication and removal of conference abstracts, 47 records were screened for inclusion in the review. Appraisal of titles and abstracts led to the exclusion of 40 studies and the further review of 7 full publications. Of the 7 full articles evaluated, 1 systematic review and 1 RCT were added at this update.

ADDITIONAL INFORMATION

Chlamydia trachomatis infection coexists in 10% to 41% of adults with gonorrhoea. Treatment with antimicrobial agents effective against potential co-existent chlamydia may additionally exert a synergistic effect and is advised whenever treating gonorrhoea. Choice of antimicrobials should be guided by local and individual isolate resistance data.

DEFINITION

Gonorrhoea is caused by infection with *Neisseria gonorrhoeae*. In men, uncomplicated urethritis is the most common manifestation, with dysuria and urethral discharge. Less typically, signs and symptoms are mild and indistinguishable from those of chlamydial urethritis. In women, the most common site of infection is the uterine cervix, infection of which results in symptoms (such as vaginal discharge, lower abdominal discomfort, and dyspareunia) in less than half of cases. **Diagnosis** Advances in nucleic acid amplification techniques (NAAT) allow testing on non-invasively collected specimens (urine and self-taken vaginal swabs). NAAT may have sensitivity of >90%, compared with 75% sensitivity of culture.^[1] However, NAAT cannot provide data on antimicrobial sensitivity, so culture and sensitivity testing are required before commencement of antimicrobial therapy. In addition, the specificity of NAAT ranges from 98.1% to 99.7%^[2] and caution is required when interpreting positive results.^[3]^[4] NAAT is also used off licence to test pharyngeal and genital sites.^[5]^[6]^[7]^[8]^[9] The sensitivity of NAAT in extragenital diagnosis is considerably greater than culture, but the specificity of extragenital NAAT is such that all reactive results need to be confirmed using a separate platform.^[10] **Resistance** Resistance to single-dose antimicrobials develops frequently and antimicrobial sensitivity of gonococcal isolates is monitored nationally to monitor and inform prescribing guidelines.^[11] Clinicians need to be aware of their local resistance profile and the resistance profiles of individual isolates to make appropriate treatment choices. All infected individuals should have a test of cure 2 weeks after treatment to ensure complete eradication of the organism. All sexual partners of infected individuals should be identified and treated concurrently (see review on Partner notification). The index patient should be advised to refrain from

sexual intercourse with any untreated partner. **Co-infection** *Chlamydia trachomatis* infection co-exists in 10% to 41% of adults with gonorrhoea.^{[12] [13] [14] [15] [16] [17]} Treatment for potential co-existent chlamydia is advised whenever treating gonorrhoea.

INCIDENCE/ PREVALENCE	In UK genitourinary medicine clinics, after a downward trajectory between 2002 and 2008, the number of diagnosed gonorrhoea infections rose by 70% between 2008 and 2012. This apparent rise in infection may be, in part, due to increased testing since the introduction of NAAT. In 2012, the incidence of gonorrhoea in the UK was 48 per 100,000. The highest prevalence was seen in adults age 20 to 24 years, at 249 per 100,000 in men and 141 per 100,000 in women. ^[18] In the UK, infection is over-represented in specific populations (men who have sex with men [MSM] and black Caribbean people), mainly in urban areas.
AETIOLOGY/ RISK FACTORS	Most gonococcal infections result from penile-vaginal, penile-rectal, or penile-pharyngeal contact. An important minority of infections are transmitted from mother to child during birth, which can cause a sight-threatening purulent conjunctivitis (ophthalmia neonatorum).
PROGNOSIS	The natural history of untreated gonococcal infection is spontaneous resolution and microbiological clearance after weeks or months of unpleasant symptoms. ^[19] During this time, there is a substantial likelihood of transmission to others and of complications developing in the infected individual. ^[19] In many women, the lack of readily discernible signs or symptoms of cervicitis means that infections go unrecognised and untreated. An unknown proportion of untreated infections causes local complications, including lymphangitis, periurethral abscess, Bartholin's abscess, and urethral stricture; epididymitis in men; and, in women, involvement of the uterus, fallopian tubes, or ovaries causing pelvic inflammatory disease (see review on Pelvic inflammatory disease). One review found that <i>N gonorrhoeae</i> was cultured from 8% to 32% of women with acute pelvic inflammatory disease in 11 European studies and from 27% to 80% of women in 8 US studies. ^[20] The proportion of <i>N gonorrhoeae</i> infections in women that lead to pelvic inflammatory disease has not been well studied. However, one study of 26 women exposed to men with gonorrhoea found that 19 women were culture-positive and, of these, 5 women had pelvic inflammatory disease and another 4 had uterine adnexal tenderness. ^[21] Pelvic inflammatory disease may lead to infertility (see review on Pelvic inflammatory disease). In some people, localised gonococcal infection may disseminate. A US study estimated the risk of dissemination to be 0.6% to 1.1% among women, whereas a European study estimated it to be 2.3% to 3.0%. ^{[22] [23]} The same European study found a lower risk in men, estimated to be 0.4% to 0.7%. ^[23] When gonococci disseminate, they cause petechial or pustular skin lesions; asymmetrical arthropathies, tenosynovitis, or septic arthritis; and rarely, meningitis or endocarditis.
AIMS OF INTERVENTION	To relieve symptoms; avoid complications; and prevent further transmission, with minimal adverse effects of treatment.
OUTCOMES	Cure rates at any site of infection, including microbiological cure rates defined as number of infected people or infected sites culture negative at least 48 hours after treatment, divided by number of infected people or infected sites cultured 1 to 14 days after treatment; and adverse effects of treatment.
METHODS	<i>Clinical Evidence</i> search and appraisal September 2013. The following databases were used to identify studies for this systematic review: Medline 1966 to September 2013, Embase 1980 to September 2013, and The Cochrane Database of Systematic Reviews 2013, Issue 10 (1966 to date of issue). Additional searches were carried out in the Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) Database. We also searched for retractions of studies included in the review. Titles and abstracts identified by the initial search, run by an information specialist, were first assessed against predefined criteria by an evidence scanner. Full texts for potentially relevant studies were then assessed against predefined criteria by an evidence analyst. Studies selected for inclusion were discussed with an expert contributor. All data relevant to the review were then extracted by an evidence analyst. Study design criteria for inclusion in this review were: published RCTs and systematic reviews of RCTs in English language, any level of blinding (including those described as 'open', 'open label', or unblinded) and where the minimum length of follow-up was 48 hours. There was no specified minimum sample size or attrition rate. We included RCTs and systematic reviews of RCTs where harms of an included intervention were assessed, applying the same study design criteria for inclusion as we did for benefits. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 12). The categorisation of the quality of the

evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of treatments for uncomplicated infections in men and non-pregnant women?

OPTION SINGLE-DOSE ANTIBIOTIC REGIMENS IN MEN AND NON-PREGNANT WOMEN

- For GRADE evaluation of interventions for Gonorrhoea, [see table, p 12](#).
- Single-dose antibiotic regimens have achieved cure rates of 95% and higher in men and non-pregnant women with urogenital or rectal gonorrhoea, although we don't know how different single-dose antibiotic regimens compare with each other. However, resistance to many widely available antibiotics (e.g., penicillins, tetracyclines, fluoroquinolones) continues to spread, making it necessary to consider local *N gonorrhoeae* susceptibility patterns when choosing a treatment regimen.

Benefits and harms

Single-dose antibiotic regimens:

We found one systematic review (search date 1993 ^[24]) and two additional RCTs. ^[25] ^[26] The first review identified studies (RCTs, controlled clinical trials, and observational studies), published from 1981 to 1993, that used a single-dose regimen based on an antimicrobial other than a beta lactamase-sensitive penicillin or a tetracycline. The second systematic review examined the effects of gentamicin only, and identified no new RCTs of interest. We found no systematic review or RCTs of single-dose antibiotics for eye infections. See Comment below for further information on adverse effects and information on single-dose antibiotics for eye infections from observational studies.

Cure rates

Single-dose antibiotic regimens compared with each other We don't know whether any one single-dose antibiotic regimen used to treat gonorrhoea is consistently more effective than any other single-dose antibiotic regimens used to treat gonorrhoea, as we found insufficient evidence from indirect comparisons derived from RCT and non-RCT data. In addition, resistance to individual single-dose antibiotic regimens may vary by location and over time ([very low-quality evidence](#)).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Cure rates					
^[24] Systematic review	At least 24,200 people or infected sites	Cure rates with single-dose antibiotics The review reported cure rates for each single-dose antibiotic assessed by combining results across individual arms of trials For full details see Comments	Significance not assessed		
^[25] RCT	105 female sex workers	Failure rates , up to 28 days 1/26 (4%) with cefixime 24/72 (32%) with ciprofloxacin Assignment ratio was 2:1 for ciprofloxacin:cefixime	P <0.01	○○○	cefixime
^[26] RCT 3-armed trial	300 people (229 men and 71 women); pregnancy not reported	Failure rate , 5 days after treatment 11/100 (11%) with ciprofloxacin (tablet) 6/100 (6%) with ceftriaxone (injection) 2/100 (2%) with spectinomycin (injection)	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		In addition, 9 people with ciprofloxacin, 4 people with ceftriaxone, and 4 people with spectinomycin had partial response only with dysuria and diplococci in pus cells			
[26] RCT 3-armed trial	300 people (229 men and 71 women); pregnancy not reported	Cure rate (clinical and laboratory) , 5 days after treatment 80/100 (80%) with ciprofloxacin (tablet) 90/100 (90%) with ceftriaxone (injection) 94/100 (94%) with spectinomycin (injection)	Significance not assessed		

Adverse effects

No data from the following reference on this outcome. [24] [25] [26]

Comment:

There is consensus that antibiotics are effective in treating gonorrhoea, and a placebo-controlled trial would be unethical. Much of the published data are based on observational studies and were not eligible for inclusion in this review. We have included one analysis previously reported in this *Clinical Evidence* review which includes both RCT and non-RCT data and combined results across individual arms of trials up to 2004. Hence, in this option, we have reported this mixed analysis, [24] and any RCTs subsequent to this date. Combining results across individual arms of trials, 97% of people were cured on the basis of culture results with any single-dose antibiotic. [24] These results do not directly compare one antibiotic with another and, therefore, should be interpreted with caution when considering superiority of one antibiotic over another. Sites of infection, when specified, included the cervix, urethra, rectum, and pharynx. Comparison of cure rates by site of infection found that cure rates were >95% for all sites except the pharynx, for which they were about 80% (see table 1, p 11). [24] [27] However, these data are old, and resistance patterns may have changed.

We also found one prospective cohort study, including 80 female sex workers not currently involved in the sex trade. [28] The study found a 25/66 (38%) failure rate with ciprofloxacin at 8 to 10 days after treatment. [28]

Gonococcal eye infections:

We found two small cohort studies (number of people ranging from 12–31) of single-dose ceftriaxone for gonococcal eye infections. [29] [30] In the first study (12 adults with conjunctivitis), all people responded well to a single 1 g dose of ceftriaxone. [29] In the second study (21 neonates with gonococcal ophthalmia), eye swabs from all neonates were negative 24 hours after a single intramuscular 62.5-mg dose of ceftriaxone. [30] Everyone responded to a single intramuscular dose of ceftriaxone. Further RCTs are unlikely.

Clinical guide:

There is good agreement between assessments of antigonococcal activity of antimicrobials *in vitro* and their efficacy in clinical trials. A large number of people were evaluated in a range of settings, suggesting that the results can be generalised. However, comparative results from different settings were not reported. Single-dose regimens may make adherence more likely. The ceftriaxone and spectinomycin regimens require intramuscular injection. Resistance is now widespread for all penicillins, sulphonamides, tetracyclines, and fluoroquinolones in many parts of the world. [25] [28] [31] [32] [33] [34] Resistance to third-generation and extended-spectrum cephalosporins is emerging, [11] [33] [35] [36] but resistance to spectinomycin is rarely reported (see table 2, p 11). [32] [34] [37] [38] [39] Single-dose regimens using fluoroquinolones, third-generation and extended-spectrum

cephalosporins, or spectinomycin are generally safe and well tolerated.^[40] The most important adverse effects are rare hypersensitivity reactions. Minor adverse effects are most troublesome for the cefixime 800-mg regimen^{[41] [42]} and the azithromycin 2-g regimen;^{[40] [43]} both cause frequent gastrointestinal upset. All the other effective doses are associated with a low incidence of adverse outcomes. One large observational cohort study of azithromycin, cefixime, ciprofloxacin, and ofloxacin in 'everyday use' found few serious adverse effects.^[44] Quinolones may cause arthropathy in animals. One systematic review of harms (search date 2000) found no irreversible fluoroquinolone-induced cartilage pathology after 0.3 to 10.0 months of follow-up in 201 adolescents treated for between 7 and 270 days.^[45]

QUESTION What are the effects of treatments for uncomplicated infections in pregnant women?

OPTION SINGLE-DOSE ANTIBIOTIC REGIMENS IN PREGNANT WOMEN

- For GRADE evaluation of interventions for Gonorrhoea, [see table, p 12](#).
- Single-dose antibiotics are effective for curing gonorrhoea in pregnant women.

Benefits and harms


Single-dose antibiotic regimens versus each other:

We found one systematic review (search date 2012,^[46] 2 RCTs,^{[47] [48]} 362 people) of treatments of gonococcal infection during pregnancy.

Cure rates

Single-dose antibiotic regimens compared with each other We don't know whether any one single-dose antibiotic regimen is consistently more effective than any other in curing gonorrhoea at 14 days in pregnant women, as we found insufficient evidence ([low-quality evidence](#)).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Cure rates					
^[47] RCT 3-armed trial	267 pregnant women with positive cultures for gonorrhoea In review ^[46] The remaining arm assessed ceftriaxone	Failure to achieve cure , 14 days 9/84 (11%) with amoxicillin plus probenecid 4/84 (5%) with spectinomycin 168 women in this analysis See further information on studies for details of cure rate by site of infection	OR 2.29 for amoxicillin plus probenecid versus spectinomycin 95% CI 0.74 to 7.08 P = 0.15 The study may have lacked power to detect clinically important differences between groups	↔	Not significant
^[47] RCT 3-armed trial	267 pregnant women with positive cultures for gonorrhoea In review ^[46] The remaining arm assessed spectinomycin	Failure to achieve cure , 14 days 9/84 (11%) with amoxicillin plus probenecid 4/84 (5%) with ceftriaxone 168 women in this analysis See further information on studies for details of cure rate by site of infection	OR 2.29 for amoxicillin plus probenecid versus ceftriaxone 95% CI 0.74 to 7.08 P = 0.15 The study may have lacked power to detect clinically important differences between groups	↔	Not significant
^[48] RCT	95 women with positive cultures for gonorrhoea In review ^[46]	Eradication rates of cervical and rectal infections 96.8% with intramuscular ceftriaxone 96.0% with oral cefixime Absolute numbers not reported See Further information on studies	Reported as not significant P value not reported	↔	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[48] RCT	95 women with positive cultures for gonorrhoea In review [46]	Eradication rates of pharyngeal infections 100.0% with intramuscular ceftriaxone 100.0% with oral cefixime Absolute numbers not reported See Further information on studies	Reported as not significant P value not reported		Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[48] RCT	Women with positive cultures for gonorrhoea In review [46]	Adverse effects 10/60 (17%) with ceftriaxone 7/62 (11%) with cefixime Adverse effects included soreness at the injection site among women receiving ceftriaxone and some 'minor' malformations among their children, generally cosmetic (e.g., nevus, café au lait spots, skin tag)	Significance not assessed		
[47] RCT 3-armed trial	267 pregnant women with positive cultures for gonorrhoea In review [46]	Adverse effects with amoxicillin plus probenecid with spectinomycin with ceftriaxone Reported vomiting after treatment in 1/267 (0.4%) women included in one trial	Significance not assessed		

Further information on studies

[47] By site of infection, amoxicillin plus probenecid cured 91% of cervical infections, 85% of rectal infections, and 80% of pharyngeal infections; ceftriaxone cured 95% of rectal and cervical infections and 100% of pharyngeal infections; spectinomycin cured 97% of rectal and cervical infections and 83% of pharyngeal infections at 14 days.

Comment:

Clinical guide:

There is consensus that antibiotics are effective in treating gonorrhoea, and that a placebo trial would be unethical. Because quinolones cause arthropathy in animals, their use is not recommended in pregnancy, although we found no reports of adverse effects of quinolones on pregnancy outcome in humans. One multicentre, prospective, controlled study (200 exposed women) found no evidence of adverse effects. [49]

QUESTION What are the effects of treatments for disseminated gonococcal infection?

OPTION MULTIDOSE ANTIBIOTIC REGIMENS FOR DISSEMINATED GONORRHOEA

- For GRADE evaluation of interventions for Gonorrhoea, [see table, p 12](#).
- We found no direct information from RCTs about multidose antibiotic regimens in the treatment of people with disseminated gonococcal infections. Consensus is that multidose antibiotic regimens are effective in disseminated gonococcal infection.

Benefits and harms

Multidose antibiotics regimens:

We found no systematic review and no RCTs of the treatment of disseminated gonococcal infection published since 1981 and no reports of adverse effects of multidose regimens using injectable cephalosporins or quinolones in this context.

Comment:

Clinical guide:

More than 100 clinical trials involving >20,000 people have found that many single-dose antimicrobial regimens cure uncomplicated infections >90% of the time. ^[24] Given the protracted natural history without treatment, this evidence suggests that treatment with these antimicrobial regimens is beneficial in disseminated disease as well. Which regimens are most beneficial cannot be determined precisely, as direct randomised comparisons of the best different regimens have not been performed. However, analysis of available trials supports the consensus that the most effective regimens are those using selected third-generation or expanded-spectrum cephalosporins and, except where resistance is common, those using selected fluoroquinolones or spectinomycin. Treatment regimens should be guided by resistance testing of each isolate. Where this is not possible, local sensitivity data should guide prescribing practice.

QUESTION What are the effects of dual treatment for gonorrhoea and chlamydia infection?

OPTION DUAL ANTIBIOTIC TREATMENT FOR GONORRHOEA AND CHLAMYDIA

- For GRADE evaluation of interventions for Gonorrhoea, [see table, p 12](#).
- We found no direct information from RCTs about the effects of dual antibiotic treatment in people with gonorrhoea and chlamydia infections. Although theory, expert opinion, and clinical experience suggest that a combination of antimicrobials active against both *N gonorrhoeae* and

C trachomatis is effective.

Benefits and harms

Dual antibiotic treatment:

We found no systematic review or RCTs on the effects of dual antibiotic treatment.

Comment:

Clinical guide:

Routine dual treatment has been advocated and implemented for the treatment of chlamydia in people with gonorrhoea and is believed to have two potential benefits. First, routine dual treatment may retard the spread of resistant gonococcal strains. Second, dual antibiotic treatment is believed to have contributed to the decline in the prevalence of chlamydia infection observed in some populations. However, other factors may also have contributed (including widespread screening for asymptomatic chlamydia infection and changes in sexual behaviour), making it difficult to directly attribute decreases in the prevalence of chlamydia infection to any specific cause. Testing for chlamydia has become more widely available, more affordable, quicker, and more sensitive than

in the past. However, despite routine testing and the use of dual antibiotic treatment, chlamydia is still found in 20% to 40% of people with gonorrhoea in many clinics. ^{[13] [14] [15] [16] [17]}

Treatment for chlamydia can cause mild gastrointestinal distress. Excess antibiotic treatment may lead to spread of resistance in *Neisseria gonorrhoeae* or other bacteria.

GLOSSARY

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Single-dose antibiotic regimens in men and non-pregnant women New evidence added. ^[26] Categorised as likely to be beneficial.

Dual antibiotic treatment for gonorrhoea and chlamydia: Evidence re-evaluated. Categorisation changed from unknown effectiveness to likely to be beneficial by consensus.

Single-dose antibiotic regimens in pregnant women One existing systematic review updated. ^[46] Categorised as likely to be beneficial.

REFERENCES

1. Van Dyck E, Ieven M, Pattyn S, et al. Detection of Chlamydia trachomatis and Neisseria gonorrhoeae by enzyme immunoassay, culture, and three nucleic acid amplification tests. *J Clin Microbiol* 2001;39:1751–1756. ^[PubMed]
2. Centre for Infections. Detection of *Neisseria gonorrhoeae* using molecular methods. September 2012. Available at <http://www.hpa.org.uk/ProductsServices/MicrobiologyPathology/UKStandardsForMicrobiologyInvestigations/TermsOfUse-ForSMIs/AccessToUKSMIs/SMIUKProtocols/smiP06DetectionofNeisseriagonorrhoeaeusing/> (last accessed 12 November 2013).
3. Palmer HM, Mallinson H, Wood RL, et al. Evaluation of the specificities of five DNA amplification methods for the detection of *Neisseria gonorrhoeae*. *J Clin Microbiol* 2003;41:835–837. ^[PubMed]
4. Katz AR, Effler PV, Ohye RG, et al. False-positive gonorrhea test results with a nucleic acid amplification test: the impact of low prevalence on positive predictive value. *Clin Infect Dis* 2004;38:814–819. ^[PubMed]
5. Ota KV, Tamari IE, Smieja M, et al. Detection of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* in pharyngeal and rectal specimens using the BD Probec Tec ET system, the Gen-Probe Aptima Combo 2 assay and culture. *Sex Transm Infect* 2009;85:182–186. ^[PubMed]
6. Schachter J, Moncada J, Liska S, et al. Nucleic acid amplification tests in the diagnosis of chlamydial and gonococcal infections of the oropharynx and rectum in men who have sex with men. *Sex Transm Dis* 2008;35:637–642. ^[PubMed]
7. Benn PD, Rooney G, Carder C, et al. Chlamydia trachomatis and Neisseria gonorrhoeae infection and the sexual behaviour of men who have sex with men. *Sex Transm Infect* 2007;83:106–112. ^[PubMed]
8. Page-Shafer K, Graves A, Kent C, et al. Increased sensitivity of DNA amplification testing for the detection of pharyngeal gonorrhea in men who have sex with men. *Clin Infect Dis* 2002;34:173–176. ^[PubMed]
9. Alexander S. The challenges of detecting gonorrhoea and chlamydia in rectal and pharyngeal sites: could we, should we, be doing more? *Sex Transm Infect* 2009;85:159–160. ^[PubMed]
10. Department of Health, Health Protection Agency, BASHH. Guidance for gonorrhoea testing in England and Wales. February 2010. Available at: http://www.bashh.org/news/478_2010-hpa-guidance-on-gonorrhoea-testing (last accessed 12 November 2013).
11. Public Health England. GRASP 2012 report: the gonococcal resistance to antimicrobials surveillance programme. October 2013. Available at: http://www.hpa.org.uk/web/HPAweb/HPAwebStandard/HPAweb_C/1317140152044 (last accessed 12 November 2013).
12. Health Protection Agency. Trends in antimicrobial resistant gonorrhoea Grasp 2008 report. June 2009. Available at: http://www.hpa.org.uk/web/HPAweb/HPAwebStandard/HPAweb_C/1245914959952 (last accessed 12 November 2013).
13. McMillan A, Manavi K, Young H. Concurrent gonococcal and chlamydial infections among men attending a sexually transmitted diseases clinic. *Int J STD AIDS* 2005;16:357–361. ^[PubMed]
14. Kent CK, Chaw JK, Wong W, et al. Prevalence of rectal, urethral, and pharyngeal chlamydia and gonorrhea detected in 2 clinical settings among men who have sex with men: San Francisco, California, 2003. *Clin Infect Dis* 2005;41:67–74. ^[PubMed]
15. Habib AR, Fernando R. Efficacy of azithromycin 1-g single dose in the management of uncomplicated gonorrhoea. *Int J STD AIDS* 2004;15:240–242. ^[PubMed]
16. Creighton S, Tenant-Flowers M, Taylor CB, et al. Co-infection with gonorrhoea and chlamydia: how much is there and what does it mean? *Int J STD AIDS* 2003;14:109–113. ^[PubMed]
17. Lyss SB, Kamb ML, Peterman TA, et al. *Chlamydia trachomatis* among patients infected with and treated for *Neisseria gonorrhoeae* in sexually transmitted disease clinics in the United States. *Ann Intern Med* 2003;139:178–185. ^[PubMed]
18. Health Protection Agency. Number and rates of selected STI diagnoses made at genitourinary medicine clinics in the UK and England: 2003–2012. Available at http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1247816547927 (last accessed 12 November 2013).
19. Hook EW, Handsfield HH. Gonococcal infections in the adult. In: Holmes KK, Mardh PA, Sparling PF, et al, eds. Sexually transmitted diseases. 3rd ed. New York: McGraw-Hill, 1999.
20. Cates WC Jr, Rolfs RT, Aral SG. Sexually transmitted diseases, pelvic inflammatory disease, and infertility: an epidemiologic update. *Epidemiol Rev* 1990;12:199–220. ^[PubMed]
21. Platt R, Rice PA, McCormack WM. Risk of acquiring gonorrhoea and prevalence of abnormal adnexal findings among women recently exposed to gonorrhoea. *JAMA* 1983;250:3205–3209. ^[PubMed]
22. Holmes KK, Wiesner PJ, Pedersen AHB. The gonococcal arthritis-dermatitis syndrome. *Ann Intern Med* 1971;75:470–471. ^[PubMed]
23. Barr J, Danielsson D. Septic gonococcal dermatitis. *BMJ* 1971;1:482–485. ^[PubMed]
24. Moran JS, Levine WC. Drugs of choice for the treatment of uncomplicated gonococcal infections. *Clin Infect Dis* 1995;20(suppl 1):47–65. Search date range 1981–1993. ^[PubMed]
25. Aplasca De Los Reyes MR, Pato-Mesola V, Klausner JD, et al. A randomized trial of ciprofloxacin versus cefixime for treatment of gonorrhea after rapid emergence of gonococcal ciprofloxacin resistance in the Philippines. *Clin Infect Dis* 2001;32:1313–1318. ^[PubMed]
26. Shams-ur-Rehman, Khan A, Amanullah, et al. Clinical efficacy of the various drugs used in the treatment of gonorrhoeae. *J Ayub Med Coll Abbottabad* 2009;21:28–30. ^[PubMed]
27. Moran JS. Treating uncomplicated *Neisseria gonorrhoeae* infections: is the anatomic site of infection important? *Sex Transm Dis* 1995;22:39–47. ^[PubMed]
28. Rahman M, Alam A, Nessa K, et al. Treatment failure with the use of ciprofloxacin for gonorrhea correlates with the prevalence of fluoroquinolone-resistant *Neisseria gonorrhoeae* strains in Bangladesh. *Clin Infect Dis* 2001;32:884–889. ^[PubMed]
29. Haimovici R, Roussel TJ. Treatment of gonococcal conjunctivitis with single-dose intramuscular ceftriaxone. *Am J Ophthalmol* 1989;107:511–514. ^[PubMed]
30. Hoosen AA, Kharsany AB, Ison CA. Single low-dose ceftriaxone for the treatment of gonococcal ophthalmia: implications for the national programme for the syndromic management of sexually transmitted diseases. *S Afr Med J* 2002;92:238–240. ^[PubMed]
31. Health Protection Agency. Diagnoses and rates of selected STIs seen at GUM clinics: 2001–2005. Available at <http://www.sepho.org.uk/viewResource.aspx?id=10468> (last accessed 12 November 2013).
32. WHO Western Pacific Gonococcal Antimicrobial Surveillance Programme. Surveillance of antibiotic resistance in *Neisseria gonorrhoeae* in the WHO Western Pacific Region, 2004. *Commun Dis Intell* 2006;30:129–132. ^[PubMed]
33. Ye S, Su X, Wang Q, et al. Surveillance of antibiotic resistance of *Neisseria gonorrhoeae* isolates in China, 1993–1998. *Sex Transm Dis* 2002;29:242–245. ^[PubMed]
34. Centers for Disease Control and Prevention. Sexually transmitted disease surveillance 2004 supplement: Gonococcal Isolate Surveillance Project (GISP) annual report – 2004. Atlanta, Georgia: US Department of Health and Human Services, December 2005. Available at <http://www.cdc.gov/std/GISP2004/> (last accessed 12 November 2013).
35. Wang SA, Lee MV, O'Connor N, et al. Multidrug-resistant *Neisseria gonorrhoeae* with decreased susceptibility to cefixime and ceftriaxone: association with genetic polymorphisms in penA, mtrR, porB1b, and ponA. *Antimicrob Agents Chemother* 2007;51:2117–2122. ^[PubMed]
36. Lindberg R, Fredlund H, Nicholas R, et al. *Neisseria gonorrhoeae* isolates with reduced susceptibility to cefixime and ceftriaxone: association with genetic polymorphisms in penA, mtrR, porB1b, and ponA. *Antimicrob Agents Chemother* 2007;51:2117–2122. ^[PubMed]
37. Dan M, Poch F, Sheinberg B. High prevalence of high-level ciprofloxacin resistance in *Neisseria gonorrhoeae* in Tel Aviv, Israel: correlation with response to therapy. *Antimicrob Agents Chemother* 2002;46:1671–1673. ^[PubMed]
38. GRASP Steering Group. The Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP) year 2005 report. London: Health Protection Agency,

2006. Available online at: www.hpa.org.uk/web/HPAweb-File/HPAweb_C/1194947380816 (last accessed 12 November 2013).
39. Fiorito S, Galarza P, Pagano I, et al. Emergence of high level ciprofloxacin resistant *Neisseria gonorrhoeae* strain in Buenos Aires, Argentina. *Sex Transm Infect* 2001;77:77.
 40. British Association for Sexual Health and HIV. National guideline on the diagnosis and treatment of gonorrhoea in adults 2005. August 2005. Available at <http://www.bashh.org/documents/116/116.pdf> (last accessed 12 November 2013).
 41. Handsfield HH, McCormack WM, Hook EW III, et al. The Gonorrhea Treatment Study Group. A comparison of single-dose cefixime with ceftriaxone as treatment for uncomplicated gonorrhea. *N Engl J Med* 1991;325:1337–1341. [PubMed]
 42. Megran DW, LeFebvre K, Willets V, et al. Single-dose oral cefixime versus amoxicillin plus probenecid for the treatment of uncomplicated gonorrhea in men. *Antimicrob Agents Chemother* 1990;34:355–357. [PubMed]
 43. Handsfield HH, Dalu ZA, Martin DH, et al. Azithromycin Gonorrhea Study Group. Multicenter trial of single-dose azithromycin vs. ceftriaxone in the treatment of uncomplicated gonorrhea. *Sex Transm Dis* 1994;21:107–111. [PubMed]
 44. Wilton LV, Pearce GL, Mann RD. A comparison of ciprofloxacin, norfloxacin, ofloxacin, azithromycin and cefixime examined by observational cohort studies. *Br J Clin Pharmacol* 1996;41:277–284. [PubMed]
 45. Burstein GR, Berman SM, Blumer JL, et al. Ciprofloxacin for the treatment of uncomplicated gonorrhea infection in adolescents: does the benefit outweigh the risk? *Clin Infect Dis* 2002;35(suppl 2):191–199. Search date 2000; primary sources Medline, and citation lists.
 46. Brocklehurst P. Antibiotics for gonorrhoea in pregnancy. In: The Cochrane Library, Issue 3, 2013. Chichester, UK: John Wiley & Sons, Ltd. Search date 2012. [PubMed]
 47. Cavenee M, Farris J, Spalding T. Treatment of gonorrhea in pregnancy. *Obstet Gynaecol* 1993;81:33–38. [PubMed]
 48. Ramus RM, Sheffield JS, Mayfield JA, et al. A randomized trial that compared oral cefixime and intramuscular ceftriaxone for the treatment of gonorrhea in pregnancy. *Am J Obstet Gynecol* 2001;185:629–632. [PubMed]
 49. Loebstein R, Addis A, Ho E, et al. Pregnancy outcome following gestational exposure to fluoroquinolones: a multicenter prospective controlled study. *Antimicrob Agents Chemother* 1998;42:1336–1339. [PubMed]

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TABLE 1 Effectiveness of selected single-dose regimens for treating gonorrhoea; published clinical trials ^[24] and comparison of cure rates at different sites of infection performed ^[27] (see text, p 4).† NOTE: These are old data and may not represent current resistance patterns

Drug and dose	Pharyngeal infections	Urogenital and rectal infections
	% cured (95% CI)	% cured (95% CI)
Ceftriaxone 250 mg	99.0 (94.4 to 100)	99.2 (98.8 to 99.5)
Ciprofloxacin 500 mg*	97.2 (85.5 to 99.9)	99.8 (98.7 to 100)
Ciprofloxacin 250 mg	88.5 (81.8 to 95.2)	98.7 (98.0 to 99.4)
Ceftriaxone 125 mg	94.1 (85.6 to 98.4)	98.9 (97.9 to 99.8)
Gatifloxacin 600 mg	100 (82.3 to 100)	99.6 (97.7 to 100)
Spectinomycin 2 g	51.8 (38.7 to 64.9)	98.2 (97.6 to 99.9)
Azithromycin 2 g	100 (82.3 to 100)	99.2 (97.2 to 99.9)
Ofloxacin 400 mg	88.7 (68.8 to 97.8)	98.6 (97.8 to 99.4)
Gatifloxacin 400 mg	100 (63.1 to 100)	99.2 (97.1 to 99.9)
Cefixime 800 mg	80.0 (51.9 to 95.7)	98.4 (95.9 to 99.6)
Cefixime 400 mg	92.3 (74.9 to 99.1)	97.4 (95.9 to 98.6)
Cefuroxime axetil 1 g	56.9 (43.3 to 70.5)	96.2 (94.8 to 97.5)
Cepodoxime proxetil 200 mg	78.9 (54.5 to 94.0)	96.5 (94.3 to 98.5)

*Excludes two published clinical trials among people known to be at high risk of harbouring fluoroquinolone-resistant strains; ciprofloxacin 500 mg cured only 48/72 (67%) of cervical infections in one trial ^[25] and 41/66 (62%) in the other. ^[28] †This analysis was undertaken by a previous contributor to this review, John Moran, based on updating the analysis of his own previously published systematic review, ^[24] and includes data up to 2004. Data subsequent to 2004 are reported separately in this *Clinical Evidence* review.

TABLE 2 Reported resistance of *N gonorrhoeae* to antimicrobials (see text, p 4).

Drug	Resistance
Sulphonamides	Widespread
Penicillins	Widespread
Tetracyclines	Widespread
Third-generation cephalosporins (e.g., ceftriaxone, cefixime)	One report from China ^[33]
Spectinomycin	Rare
Quinolones	Widespread

GRADE Evaluation of interventions for Gonorrhoea.

Important outcomes					Cure rates				
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
<i>What are the effects of treatments for uncomplicated infections in men and non-pregnant women?</i>									
unclear (at least 24,605) ^[24] ^[25] ^[26]	Cure rates	Single-dose antibiotic regimens	4	−2	0	−1	0	Very low	Quality points deducted for inclusion of non-RCT data and incomplete reporting of results; directness point deducted for no direct analysis between groups in most studies
<i>What are the effects of treatments for uncomplicated infections in pregnant women?</i>									
2 (362) ^[46] ^[47] ^[48]	Cure rates	Single-dose antibiotic regimens versus each other	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results; directness point deducted for small number of comparisons
We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.									